Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 6880 – 6892
Received 05 March 2021; Accepted 01 April 2021.

Ligand Based Designing, Synthesis and PTP1B Inhibitory Activity of Some Chalcone Derivatives

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ABSTRACT

Inhibition of enzyme is considered one of the rationale approaches to treat many diseases and Protein tyrosine phosphatase 1B (PTP1B) is one such type of target for the treatment of diabetes. It is believed that inhibition of PTP1B alters insulin resistance thus imparts therapeutic benefits in Type 2 diabetes mellitus (T2DM). Computer aided approaches of drug design and virtual modeling described some structural features must be present in PTPIB inhibitory agent. Considering this we designed and synthesized some chalcones and their heterocyclic derivatives as PTP1B inhibitors. Designed ligands were evaluated for their ability to interacts with 3D crystal structure of PTP1B enzyme using molecular docking study; compounds **AJ-9** ((*E*)-3-(3,4-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one) and **AJ-10** ((*E*)-3-(furan-2-yl)-1-(4-hydroxyphenyl)prop-2-en-1-one) exhibited desired interactions with PTP1B receptor in molecular docking study. Furthermore synthesized compounds were also tested for their enzyme (PTP1B) inhibitory activity using *in-vitro* colourimetric assay kit. Compound **AJ-10** was observed as most potent enzyme inhibitor with 62.87 % inhibition of PTP1B during *in-vitro* assay. Study suggested prominent anti-hyperglycemic potential of tested compounds.

KEYWORDS: Diabetes, Anti-hyperglycemic; PTP1B; Chalcone; Heterocycles; Insulin.

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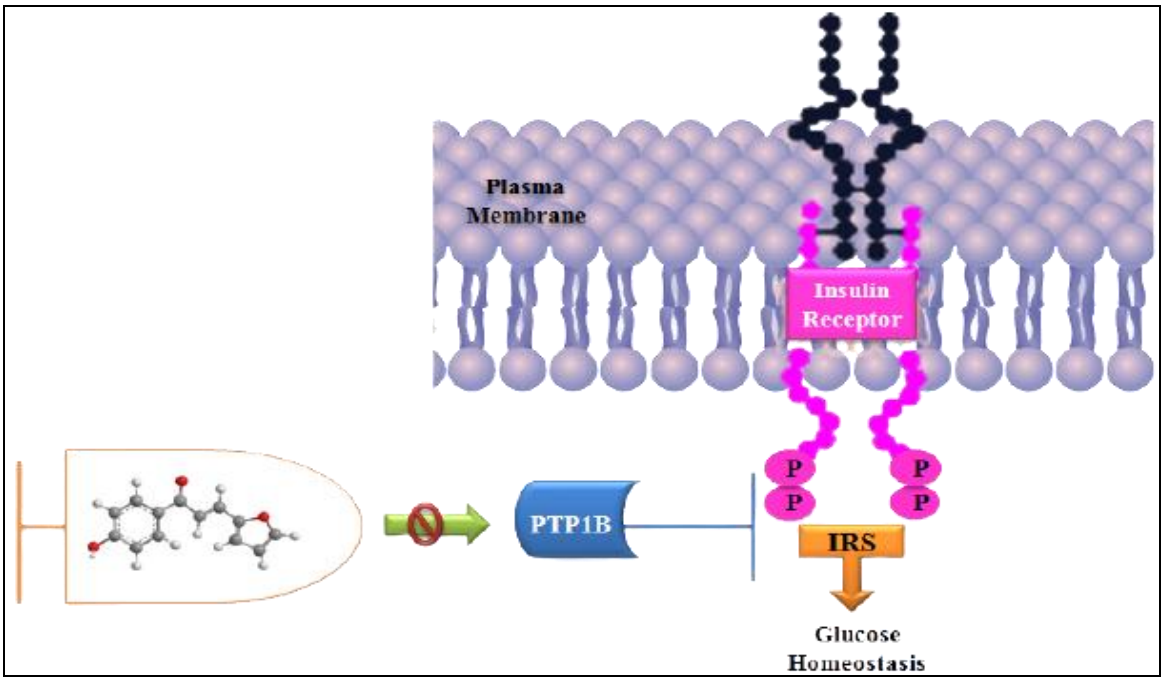

Graphical Abstract

INTRODUCTION

Protein tyrosine phosphatase 1B is non-transmembrane protein tyrosine phosphatase which significantly involved in the metabolic signaling pathways and considered as promising drug target for type 2 diabetes [1]. The literature study also proved involvement of PTP1B in negative control of insulin and leptin receptor [2]. It is believed that altered insulin sensitivity and insulin receptor dephosphorylation by PTP1B leads cascade of type 2 diabetes mellitus. PTP1B mainly expressed in tissues responsible for glucose metabolism i.e; liver, muscle and adipose tissues [3]. Studies revealed that PTP1B inhibition can modify level of insulin resistance as well as reduces effect of negative regulation of signaling pathway. Therefore it was proposed that PTP1B inhibitors can reverse insulin and leptin resistance, thus helps in metabolic disorder associated with insulin regulation like type 2 diabetes mellitus [3, 4].

Chalcones is chemically 1,3-diaryl-2-propen-1-ones in which two aromatic rings joined by a α,β-unsaturated carbonyl system. Many researchers investigated biological activities of chalcone derivatives in past few years since these compounds offers appreciable therapeutic responses in many diseases due to their specific structural diversity [5-7].

Similarly heterocyclic derivatives are well known compounds of medicinal importance and many researchers reported their antimicrobial & anticancer [8], anti-inflammatory [9] and analgesic

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activities [10] in past few years.

Considering this we planned to design & synthesize some chalcones and their heterocyclic derivatives as PTP 1B inhibitors, expected further to elicit anti-hyperglycemic response. The 3D crystal structure (PDB ID: 1Q1M) of PTP 1B receptor retrieved from RCSB (Research Collaboratory for Structural Bioinformatics) data source. The co-crystallized ligand; "5-{2-fluoro-5-[3-(3-hydroxy-2-methoxycarbonyl-phenoxy)-propenyl]-phenyl}-isoxazole-3-carboxylic acid" bound with enzyme as depicted in **Figure 1**. The interactions of bound co-crystallized ligand with amino acid residues of enzyme considered essential for PTP 1B inhibitory activity and on this basis ligands were designed and evaluated further. Chalcone and their heterocyclic derivatives were designed and evaluated for their possible interactions with binding sites of 3D crystal structure of enzyme using molecular docking (Maestro) study. These ligands showed desired interactions with enzyme's sites similar to co-crystallized ligand synthesized further and tested for their PTP 1B inhibitory activity using *in vitro* assay kit.

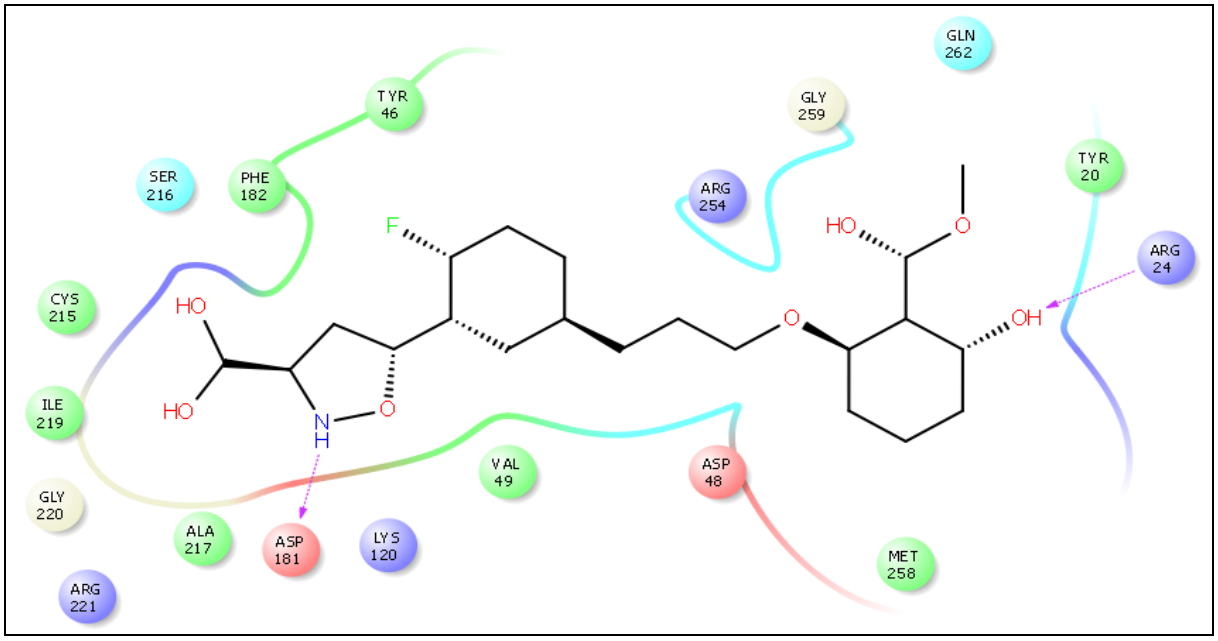

Figure 1: Interaction between ligand and PTP1B enzyme in the co-crystallized enzyme inhibitor complex (PDB ID: 1Q1M, 2.3 Å).

EXPERIMENTAL

Molecular docking studies

Crystal structure (PDB codes: 1Q1M) of enzyme PTP1B was retrieved from RCSB Protein Data Bank and subjected for optimization in protein preparation tool. Hydrogen atoms were added,

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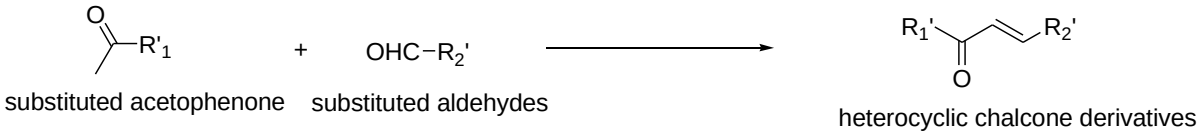
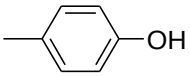
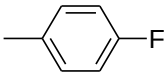
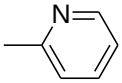
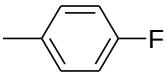
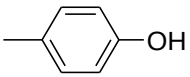
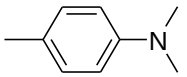
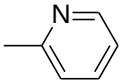
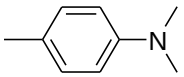
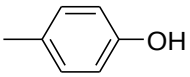
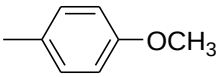
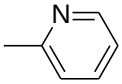
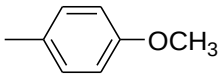
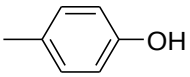
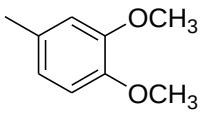
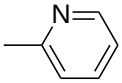
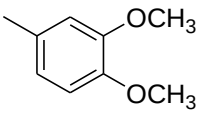
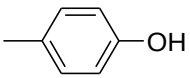
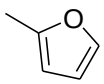
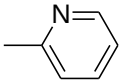
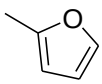
water molecules were removed and bonds orders sequences were corrected. The important amino acids residues assigned as protonated and considered essential for interactions. Force field model (OPLS 2005) was employed to optimize heavy atoms with in required RMSD (0.3). Binding positions of co-crystallized enzyme inhibitor complex were used to generate receptor grid, generation of receptor grid facilitates fixation of active site of enzyme [11, 12]. Standard precision mode of Glide docking was used in Schr¨odinger software to perform molecular docking study.

Chemistry

The target derivatives were synthesized as mentioned in **scheme 1**, using Claisen-Schmidt reaction between substituted benzaldehyde and acetophenone.



Scheme 1: Synthetic route used for proposed derivatives

Compound Code	R_1'	R_2'	Compound Code	R_1'	R_2'
AJ-6			AD-6		
AJ-7			AD-7		
AJ-8			AD-8		
AJ-9			AD-9		
AJ-10			AD-10		

Synthesis of chalcones derivatives (AJ6-AJ10)

Solution of sodium hydroxide (30%) in water and rectified spirit was placed in a flask

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 6880 – 6892
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immersed in an ice bath. Substituted acesstophenone was added with constant stirring followed by addition of substituted benzaldehydes. The mixture was stirred vigorously until to become thick (approx. 6 hr) and during this process temperature of reaction mixture was maintained about 25^0C. Thereafter mixture was refrigerated overnight and product was filtered using buchner funnel, washed and dried. The crude and dried product was recrystallized using ethanol.

Synthesis of heterocyclic derivatives of chalcones (AD6-AD10)

Mixture of substituted benzaldehydes and 4-acetylpyridine in ethanol stirred followed by addition of 40% solution of potassium hydroxide, during the process temperature of medium was maintained around 20 to 25^0C. The mixture was stirred for 6 h, thereafter cooled & refrigerated overnight. Finally reaction mixture was poured into crushed ice and acidified with dilute HCl, the precipitate of compounds (AD6-AD10) filtered, dried and recrystallized using rectified spirit.

***In vitro* PTP1B enzyme inhibitory activity**

In vitro PTP1B enzyme inhibitory activity of synthesized compounds were performed using colourimetric, PTP1B Tyrosine Phosphatase Assay Kit obtained from Merck Millipore. The activity was performed in a view to confirm possible anti-hyperglycemic profile of synthesized derivatives. Suramin provided in assay kit was served as controlled drug while human recombinant utilized in assay kit to perform PTP1B enzyme inhibitory activity. Manufacturer's protocol was followed to perform *in vitro* enzyme inhibitory activity using 96 well plate microtiter [13]. The inhibitory activity of test compounds were calculated as percentage inhibition of PTP1B enzyme, considering activity of control as 100 % using following formula:

$$\% \text{ Activity} = \frac{[\text{Test Sample (nmol}PO_4^{-2}\text{)-time zero (nmol}PO_4^{-2}\text{)}]}{[\text{Control (nmol}PO_4^{-2}\text{)-time zero (nmol}PO_4^{-2}\text{)}]} \times 100$$

RESULT AND DISCUSSION

Molecular docking studies

Computer-aided virtual screening was performed to ensure interactions between designed ligands and crystal structures of PTP1B receptor. These interactions give prediction about probable enzyme (PTP1B) inhibitory activity of compounds. The co-crystallized ligand showed some vital interactions in enzyme inhibitor complex with active sites of enzyme and these interactions were considered important for enzyme inhibitory activity of tested compounds. The proposed compounds were expected to offers similar interactions with receptor as like co-crystallized ligands. Protein preparation wizard of Schr¨odinger suite was used to prepare crystal structure of PTP1B and glide docking was used in standard precision mode to confirm binding interactions of compounds with

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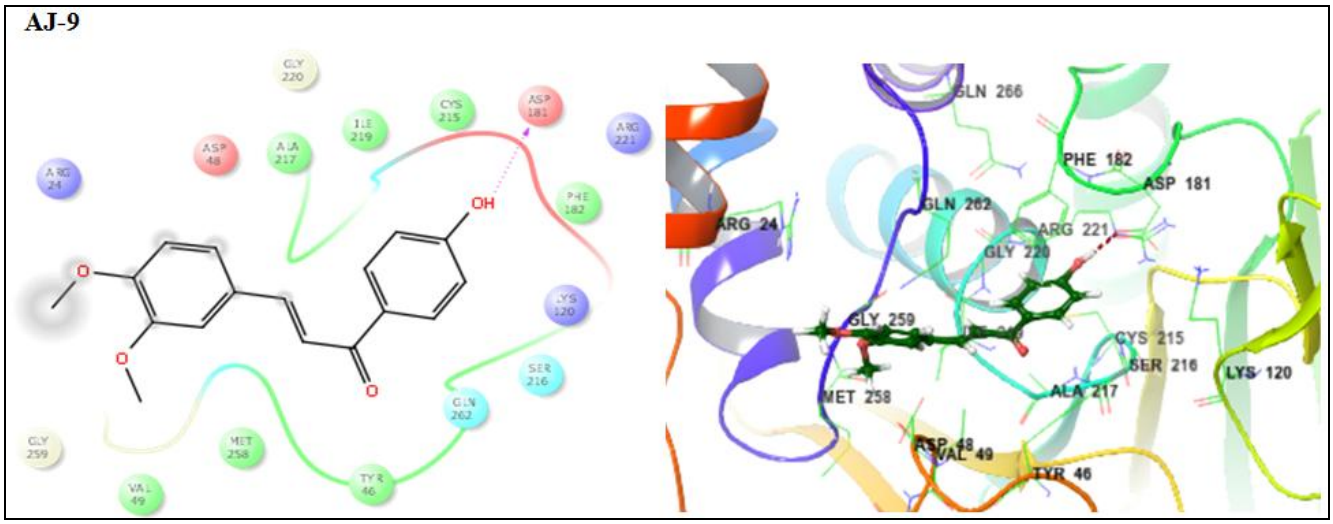
active sites of PTP1B [12].

Literature study suggested some sub-pockets (A, B and C) in the closed proximity as active sites of PTP1B responsible for insulin signaling functioning [14, 15]. Fortunately chalcone derivatives (AJ6-AJ10) showed interaction only in site A of enzyme; additionally compounds **AJ-9** ((*E*)-3-(3,4-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one) & **AJ-10** ((*E*)-3-(furan-2-yl)-1-(4-hydroxyphenyl)prop-2-en-1-one) exhibited interactions with active sites of enzyme similar in manner as depicted by co-crystallized ligand in enzyme inhibitor complex (**Figure 1**). These chalcone compounds (**AJ-9** & **AJ-10**) interacts with Asp181 in catalytic site A (**Figure 2)**. The observation of study clearly indicated that potent compounds (**AJ-9** & **AJ-10)** as well as co-crystallized ligand showed interaction with same amino acid residue (Asp181). Study observed that in enzyme inhibitor complex co-crystallized ligand interacted with Asp181 through –NH group of heterocyclic ring, while in case of designed ligands –OH group of compounds **AJ-9** & **AJ-10** bound with same amino acid residue. The docking study suggested that proposed derivatives exhibited prominent interactions and compounds **AJ-9** & **AJ-10** binds almost in similar manner (Fig. 2) as like co-crystallized ligand bound with crystal structure of PTP1B enzyme (Fig. 1). These ligands-receptor interactions ensure probability of PTP1B inhibitory activity of proposed compounds.



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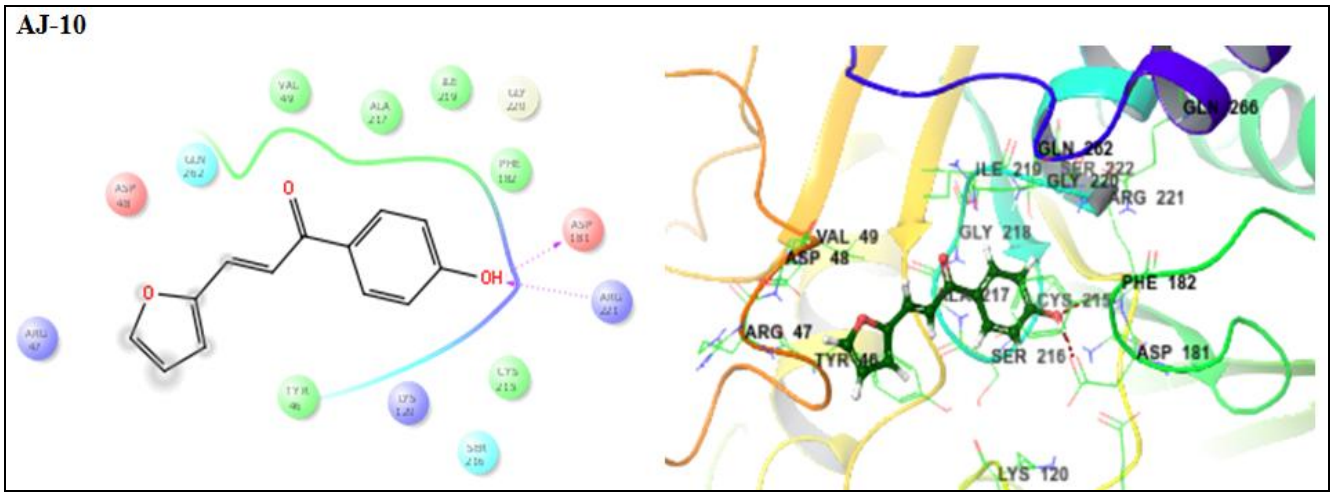

Figure 2. Binding mode of compound **AJ-9** & **AJ-9** at PTP1B binding site (PDB ID: 1Q1M). Important amino acids are depicted as sticks, whereas the lead ligand is shown in green colour with nitrogen and oxygen atom in blue and pink, respectively. Brown dotted lines represent hydrogen bonding in the active site of PTP1B.

Chemistry

Chalcone derivatives (AJ6-AJ10) were prepared using 4-hydroxy acetophenone and substituted benzaldehydes while heterocyclic derivatives of chalcone (AD6-AD10) were prepared using mixture of 4-acetylpyridine and substituted benzaldehydes. Melting points were determined using capillary melting point apparatus (Lab Hosp). The progress of reaction checked using thin layer chromatography (TLC) which was performed on silica Gel G coated plate. Physicochemical characteristics of synthesized derivatives were mentioned in **Table 1**.

Table 1. Physicochemical characteristics of synthesized derivatives.

Compound Code	Molecular Formula	TLC	M.P.
AJ-6	$C_{15}H_{11}FO_2$	Rf= 0.49	165-167°C
AJ-7	$C_{17}H_{17}NO_2$	Rf= 0.55	198-200°C
AJ-8	$C_{16}H_{14}O_3$	Rf= 0.59	185-187°C
AJ-9	$C_{17}H_{16}O_4$	Rf= 0.6	200-202°C
AJ-10	$C_{13}H_{10}O_3$	Rf= 0.47	158-160°C
AD-6	$C_{14}H_{10}FNO$	Rf= 0.44	126-128°C

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AD-7	$C_{16}H_{16}N_2O$	Rf= 0. 48	168-170°C
AD-8	$C_{15}H_{13}NO_2$	Rf= 0.46	156-158°C
AD-9	$C_{16}H_{15}NO_3$	Rf= 0.52	180-182°C
AD-10	$C_{12}H_9NO_2$	Rf= 0.51	118-120°C

Rf* value in solvent system: chloroform:ethylacetate (2:3)

IR spectra were recorded in using KBr pellet method on MB3000 (Make-ABB Bomen) spectrometer. Spectral analysis performed to establish structural characteristics of synthesized compounds. The ^{1}H-NMR spectra were recorded on Avance II 400 (Make-Bruker) NMR spectrometer and Mass spectra were recorded on Jeol SX-102 (Make-Waters) spectrometer.

(E)-1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one ***(AJ6)***

Yield 55 %,

1H NMR: δ 6.74 (1H, d, J = 15.7 Hz), 6.87 (2H, ddd, J = 8.3, 1.1, 0.4 Hz), 7.38-7.55 (6H, 7.44 (tt, J = 7.2, 1.3 Hz), 7.50 (d, J = 15.7 Hz), 7.45 (dddd, J = 7.9, 1.6, 1.3, 0.5 Hz), 7.43 (dddd, J = 7.9, 7.2, 2.0, 0.5 Hz)), 7.58 (2H, ddd, J = 8.3, 1.8, 0.4 Hz).

Mass spectra: m/e: 243.2.

(E)-3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one ***(AJ7)***

Yield 41 %,

1H NMR: 6.87 (2H, ddd, *J* = 8.3, 1.1, 0.4 Hz), 7.44-7.57 (5H, 7.49 (d, *J* = 15.7 Hz), 7.53 (ddd, *J* = 8.1, 1.4, 0.5 Hz), 7.54 (ddd, *J* = 8.1, 1.2, 0.5 Hz).

Mass spectra: m/e: 268.2

(E)-3-(2-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one ***(AJ8)***

Yield: 69

1H NMR: δ 6.70 (1H, d, *J* = 15.7 Hz), 6.87 (2H, ddd, *J* = 8.3, 1.1, 0.4 Hz), 7.44-7.57 (5H, 7.49 (d, *J* = 15.7 Hz), 7.53 (ddd, *J* = 8.1, 1.4, 0.5 Hz),

Mass spectra: m/e: 255.2

(E)-1-(4-hydroxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one ***(AJ9)***

Yield: 68

1H NMR: 7.44-7.57 (5H, 7.49 (d, *J* = 15.7 Hz), 7.53 (ddd, *J* = 8.1, 1.4, 0.5 Hz), 7.54 (ddd, *J* = 8.1,

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1.2, 0.5 Hz)), 7.58 (2H, ddd, *J* = 8.3, 1.8, 0.4 Hz)

Mass spectra: m/e: 285.2

(E)-1,3-bis(4-hydroxyphenyl)prop-2-en-1-one ***(AJ10)***

Yield: 50

1H NMR: δ 6.66 (1H, d, *J* = 15.6 Hz), 6.83-6.93 (4H, 6.86 (ddd, *J* = 8.3, 1.1, 0.4 Hz), 6.89 (ddd, *J* = 8.0, 1.7, 0.4 Hz)), 7.49-7.61 (3H, 7.53 (d, *J* = 15.6 Hz), 7.58 (ddd, *J* = 8.3, 1.8, 0.4 Hz)), 7.54 (2H, ddd, *J* = 8.0, 1.9, 0.4 Hz).

Mass spectra: m/e: 215.2

(E)-3-phenyl-1-(pyridin-4-yl)prop-2-en-1-one ***(AD-6)***

Yield: 64

1H NMR: δ 6.84 (1H, d, *J* = 15.6 Hz), 7.45-7.60 (5H, 7.52 (tt, *J* = 7.4, 1.5 Hz), 7.49 (dddd, *J* = 8.5, 1.6, 1.5, 0.4 Hz), 7.55 (dddd, *J* = 8.5, 7.4, 1.4, 0.4 Hz)), 7.75-7.84 (3H, 7.82 (ddd, *J* = 4.6, 1.6, 0.5 Hz), 7.80 (d, *J* = 15.6 Hz)), 8.74 (2H, ddd, *J* = 4.6, 1.9, 0.5 Hz).

Mass spectra: m/e: 228.2

(E)-3-(4-chlorophenyl)-1-(pyridin-4-yl)prop-2-en-1-one ***(AD7)***

Yield: 44

1H NMR: 7.52 (2H, ddd, *J* = 8.7, 1.3, 0.5 Hz), 7.74 (2H, ddd, *J* = 8.7, 1.8, 0.5 Hz), 7.74-7.83 (3H, 7.81 (ddd, *J* = 4.6, 1.6, 0.5 Hz).

Mass spectra: m/e: 253.2

(E)-3-(2-chlorophenyl)-1-(pyridin-4-yl)prop-2-en-1-one ***(AD8)***

Yield: 63

1H NMR: 7.39 (1H, ddd, *J* = 8.1, 7.6, 1.5 Hz), 7.47-7.57 (2H, 7.52 (ddd, *J* = 8.3, 1.5, 0.5 Hz), 7.52 (ddd, *J* = 8.3, 7.6, 1.4 Hz)), 7.74-7.83 (3H, 7.81 (ddd, *J* = 4.6, 1.6, 0.5 Hz), 7.78 (d, *J* = 15.6 Hz).

Mass spectra: m/e: 240.2

(E)-3-(3-nitrophenyl)-1-(pyridin-4-yl)prop-2-en-1-one ***(AD9)***

Yield: 62

1H NMR: δ 6.78 (1H, d, *J* = 15.6 Hz), 7.39 (1H, ddd, *J* = 8.1, 7.6, 1.5 Hz), 7.47-7.57 (2H, 7.52 (ddd, *J* = 8.3, 1.5, 0.5 Hz), 7.52 (ddd, *J* = 8.3, 7.6, 1.4 Hz)), 7.74-7.83 (3H, 7.81 (ddd, *J* = 4.6, 1.6, 0.5 Hz).

Mass spectra: m/e: 270.2

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Received 05 March 2021; Accepted 01 April 2021.

(E)-3-(4-hydroxyphenyl)-1-(pyridin-4-yl)prop-2-en-1-one ***(AD10)***

Yield: 54

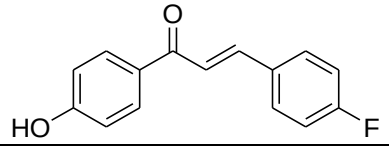
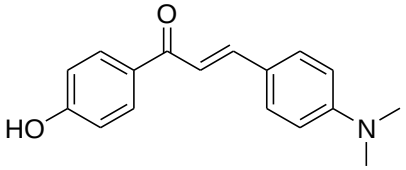
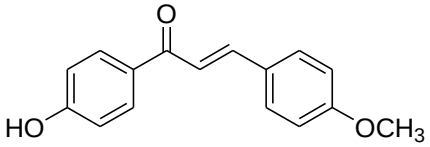
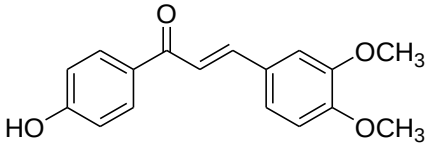
1H NMR: 6.87 (ddd, *J* = 8.3, 1.1, 0.4 Hz)), 7.59 (2H, ddd, *J* = 8.3, 1.8, 0.4 Hz), 7.73-7.83 (3H, 7.81 (ddd, *J* = 4.6, 1.6, 0.5 Hz), 7.77 (d, *J* = 15.6 Hz).

Mass spectra: m/e: 200.2

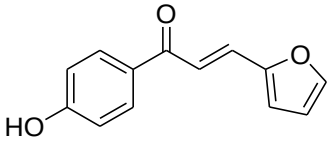
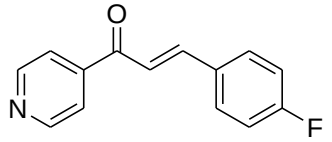
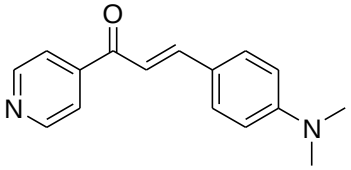
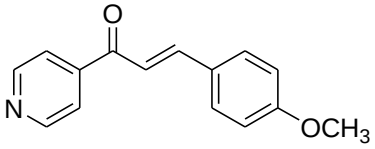
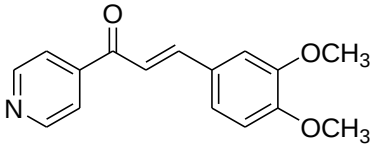
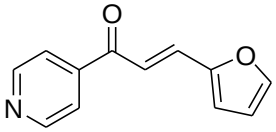
In vitro **PTP1B enzyme inhibitory activity**

The synthesized compounds further tested for their PTP1B enzyme inhibitory activity using *in vitro* assay kit as per the manufacturer's protocol [13]. The synthesized compounds were evaluated at 30 µM concentration. Compounds those exhibited appreciable interactions in molecular docking study also showed ≥ 50 % inhibition of PTP1B enzyme; compound **AJ-9** and **AJ-10** showed 52.81% and 62.87% inhibition of enzyme PTP1B respectively. However heterocyclic derivatives (**AD6-AD10**) were not observed as potent inhibitory agents as mentioned in **Table 2**. Prominent inhibition of PTP1B directly resembles probable anti-hyperglycemic response, therefore potent compounds (**AJ-9** and **AJ-10**) can be used as lead to develop synthetic anti-hyperglycemic agents which can exert their effect *via* insulin signaling pathway.

Table 2: Results of *in-vitro* PTP1B enzyme inhibitory activity:

S. No.	Compound code	Structure of target derivatives	% Inhibitory activity (30 µM)
1	AJ-6		23.70
2	AJ-7		29.95
3	AJ-8		42.16
4	AJ-9		52.81

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 6880 – 6892
Received 05 March 2021; Accepted 01 April 2021.

5	AJ-10		62.87
06	AD-6		41.21
07	AD-7		46.14
08	AD-8		49.12
09	AD-9		38.09
10	AD-10		47.18
11	Suramin		23.04 (10 μM)

CONCLUSION

In summary, chalcone and their heterocyclic derivatives were designed, synthesized and evaluated for their PTP1B inhibitory activity. Ligands were designed on the basis of prerequisite structural features obtained from ligand (co-crystallized) receptor complex retrieved from RCSB data sources. The designed ligands showed interactions with catalytic site therefore synthesized further and evaluated for their *in-vitro* Protein Tyrosine Phosphatase 1B inhibitory potential using calorimetric assay kit. Compounds **AJ-9** & **AJ-10** were found as potent inhibitory agent against PTP1B (inhibition ≥ 50%). The most active compound **AJ-10** exhibited 62.87 % inhibition of enzyme PTP1B and as indicated by molecular docking study this compound also interact remarkable with active site of enzyme. Therefore potent derivative possesses scope of further development as promising anti-hyperglycemic agents.

ACKNOWLEDGEMENT

The authors acknowledged Director, IISER-Bhopal for facilitating spectral analysis of the

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 6880 – 6892
Received 05 March 2021; Accepted 01 April 2021.

compounds reported in this work.

CONFLICT OF INTEREST: No conflict of interest associated with this work

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